*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

# CETP Inhibitors (Cetrapibs)

**Evidence Summary**

Gene variants that reduce CETP activity have been associated with cardioprotection. CETP inhibitors have generally been found to be safe, but have not reliably shown a protective effect in RCTs.

**Neuroprotective Benefit:** CETP lowering gene variants have been associated with reduced risk of cognitive decline in a subset of ethnic populations, with effects modified by ApoE4. The effect of cetrapibs on brain health is unknown.

**Aging and related health concerns:** Potential cardiovascular benefits of cetrapibs are likely related to lowering LDL-C rather than raising HDL-C. Consistent benefits have not yet been seen with cetrapibs in Phase 3 RCTs.

**Safety:** Cetrapibs have been well-tolerated in clinical trials with adverse event profiles largely similar to placebo, though some show elevations on an inflammation marker. Blood pressure elevations with torcetrapib were related to off-target effects.

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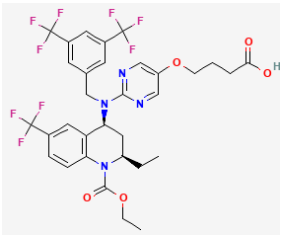
|---|---|---|
| **Availability**: In clinical trials | **Dose**: Not established<br>Dalcetrapib is being tested at 600 mg/day orally.<br>Obicetrapib is being tested at 10 mg/day orally. | **Obicetrapib**<br>**Chemical formula:** $C_{32}H_{31}F_9N_4O_5$<br>**MW**: 722.6 g/mol<br>  <br>Source: PubChem |
| **Half-life**:<br>Obicetrapib: Terminal $T_{1/2}$ is between 121 and 151 hours at doses from 1-25 mg in healthy adults.<br>Dalcetrapib: Terminal $T_{1/2}$ is ~30 hours | **BBB**: N/A | |
| **Clinical trials**: Anacetrapib, Dalcetrapib, Evacetrapib, and Torcetrapib failed in Phase 3 RCTs for cardiovascular disease including ~30,000 participants/trial. Obicetrapib has been tested in Phase 2 RCTs (n=97; 120; 364) and is currently being tested in Phase 3 trials for cardiovascular disease. | **Observational studies**: Gene variants in CETP have been associated with cardiovascular disease risk, longevity, and Alzheimer's disease in some ethnic groups.<br>CETP inhibitors have been associated with reduced risk for newly onset diabetes based on meta-analyses from RCTs. | |

**What is it?**

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that is produced in the liver which is involved in the transport of cholesterol esters and triglycerides between lipoproteins [1]. It typically facilitates the exchange between triglycerides on very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) particles with cholesterol esters on high-density lipoproteins (HDL) particles. Through this activity, CETP indirectly participates in the process of reverse cholesterol transport, whereby excess cholesterol from cells is taken up by HDL particles and is transported to the liver for excretion, by facilitating the regeneration of small HDL particles with the capacity to pick up more cholesterol. However, CETP activity can also lead to a net shift in the cholesterol profile from HDL to LDL, which is considered atherogenic. Genetic variants in CETP which reduce its activity have been associated with elevated HDL-cholesterol levels and cardioprotection in a variety of observational studies, though the

protective effects are highly influenced by genetic background and lifestyle factors [2]. Based on the hypothesis that inhibiting CETP would mimic this cardioprotective effect, various companies have developed CETP inhibitors. This class of drugs is referred to as cetrapibs. Four cetrapibs have been tested in Phase 3 clinical trials, but the majority of these studies were terminated due to futility. Obicetrapib, which is considered to have better potency and bioavailability relative to prior cetrapibs, is currently being tested in Phase 3 RCTs [1].

Clinically tested cetrapibs:

***Anacetrapib*** is the only CETP inhibitor to date to show efficacy in reducing cardiovascular events and mortality in a Phase 3 RCT. The REVEAL trial also had a longer follow-up period relative to other trials, which is thought to have played a role in the positive result. Anacetrapib was in clinical development by Merck, but development was terminated due to evidence that it accumulated in adipose tissue, which may be related to the poor solubility of this compound.

***Dalcetrapib*** is considered the least potent CETP inhibitor tested in Phase 3 RCTs, due to its modest effects on altering the blood lipoprotein profile relative to other clinically tested CETP inhibitors. The Phase 3 dal-OUTCOMES trial was terminated early due to lack of efficacy. Based on this study, Roche halted its clinical development of dalcetrapib, but the asset was later acquired by Dalcor, which is currently tested the drug in a Phase 3 RCT in a genetically defined population with acute coronary syndrome.

***Evacetrapib*** is a CETP inhibitor that was under clinical development by Eli Lilly & Company, but development was halted after the Phase 3 ACCELERATE trial was terminated early due to futility.

***Torcetrapib*** is a CETP inhibitor that was under clinical development by Pfizer, but development was terminated after it was associated with an increased rate of adverse cardiovascular events and mortality in the Phase 3 ILLUMINATE trial. These adverse effects were attributed to off target effects on the aldosterone system, leading to elevated blood pressure.

***Obicetrapib*** was originally developed by Dezima, which was subsequently acquired by Amgen. Amgen licensed out obicetrapib to NewAmderstam Pharma in 2020. Obicetrapib is currently being tested in Phase 3 clinical trials for atherosclerotic cardiovascular disease and familial hypercholesteremia.

***MK-8262*** is a CETP inhibitor that was developed by Merck. Preclinical and Phase 1 studies suggest that this compound may have a better pharmacokinetic and prospective safety profile relative to other clinically tested CETP inhibitors [3]. However, development of anacetrapib was prioritized, such that MK-8262 was never tested in later phase efficacy studies.

Commonly studied CETP gene variants:

Taq1B (rs708272, G→A) involves a silent based change from G (B1 allele) to A (B2 allele) at the 277th nucleotide in intron one of the CETP gene [4]. Its name is derived from this location possessing a restriction site for the endonuclease Taq1 with the wildtype (B1) allele. The B2 allele has been associated with reduced CETP activity and elevated HDL-cholesterol (HDL-C) levels. Since this is a silent change in terms of amino acid coding, the effects are thought to stem from linkage disequilibrium between this variant and another functional CETP variant. The C-629A variant in the promoter region has been shown to be in linkage disequilibrium with Taq1B in some ethnic groups and is hypothesized to mediate the effects associated with the Taq1B variant.

-629 (rs1800775; C→A) is located in the promoter region of CETP at a Sp1/Sp3 transcription factor binding site [5]. This variant (A) has been associated with reduced CETP expression and elevated HDL-C levels.

I405V (rs5882; G→A) involves an amino acid coding change from isoleucine to valine at codon 405 in exon 14 of the CETP gene [6]. The V allele has been associated with reduced CETP levels and higher levels of HDL-C.

**Neuroprotective Benefit:** CETP lowering gene variants have been associated with reduced risk of cognitive decline in a subset of ethnic populations, with effects modified by ApoE4. The effect of cetrapibs on brain health is unknown.

*Types of evidence:*

- 2 meta-analyses of gene case-control studies for CETP gene variants and dementia risk
- 2 prospective cohort studies for CETP gene variants and dementia risk
- 3 cohort studies for CETP gene variants and brain structure measures
- 1 case-control study for CETP gene variants and circulating brain lipids

- 1 case-control study assessing relationship between CETP levels and cognition
- I cohort study for CETP gene variants and cognition

***Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function***:

Due to the heart-brain connection, cardiovascular disease and associated risk factors can also impact future dementia risk. The modulation of CETP activity could impact the brain via the health and function of the brain vasculature. CETP inhibitors have been tested in clinical trials in the context of cardiovascular disease, however, these trials did not assess cognitive measures. Due to the relatively short duration of treatment and follow-up, a potential impact on dementia incidence rates has also not been investigated. While the failure of CETP inhibitors on cardiovascular endpoints in Phase 3 trials to date suggests that an impact to cognitive health is also unlikely, the sources of CETP are different in the brain and periphery, such that CETP activity may play distinct roles in the central and peripheral compartments [7]. Furthermore, since the failures of the previously tested compounds are thought to be compound-related rather than target-related [8], the potential effects on cognition of newer, optimized, CETP inhibitors, which positively impact cardiovascular health, remain unknown.
The current evidence regarding a potential role for CETP on cognitive decline stems from gene association studies regarding a variety of CETP gene variants. The heterogeneity seen across studies likely reflects that the impact of CETP on brain structure and dementia risk is relatively small, such that it is highly influenced by other gene and environmental interactions [9; 10]. As a result, effects have been more apparent in homogenous populations, and populations with different genetic backgrounds living in different parts of the world often show different associations with respect to a particular CETP gene variant. Additionally, the associations with some of the variants appear to be impacted by age, such that the same allele could be associated with neuroprotection in youth but with neurodegeneration during aging [11]. A major limitation of the gene association studies is that most do not assess the functional consequence of the CETP gene variant on brain or lipid profile measures in the study population, as some studies have found that the same variant can impact blood lipid profiles in opposite ways in response to an environmental exposure, such as dietary intervention, in different populations [2]. Consequently, it is unclear whether there is a particular set of genetic and environmental conditions under which lower levels of CETP are neuroprotective. Furthermore, it is unclear how well these genetic variants linked to lower levels of CETP activity would translate in terms of the impact of CETP inhibitors on cognitive outcomes. The nature of CETP inhibition from genetic variants confers a low-to-moderate

levels of inhibition across the lifespan, whereas CETP inhibitors conger a high degree of inhibition starting later in life, with the current target population in middle age or late life.

***CETP gene variants and dementia risk***:

The initial association between CETP hypofunctional variants with longevity, cognition, and reduced dementia risk stems from a study in the Ashkenazi Jewish population [12]. This population has relatively high genetic homogeneity, which may explain why the association was apparent in this population, but absent in other cohorts using more genetically mixed populations. Additionally, or alternatively, the I405V CETP variant may confer a particular advantage in this population relative to other ethnic groups due to their genetic background and/or other lifestyle factors.

In a population of Ashkenazi Jews (n=158) with exceptional longevity (age 99.2 ± 0.3 years), individuals with normal cognition (MMSE >25) were more likely to be homozygous for the V allele of the I405V (rs5882 G>A) single nucleotide polymorphism (SNP) in the CETP gene (29% vs 14%, p = 0.02), which resulted in a lower level of CETP expression (1.73 ± 0.11 vs 2.12 ± 0.10 µg/mL, p = 0.01), higher levels of HDL and larger lipoprotein particles [12]. A similar association was found with the VV genotype, higher HDL levels, larger particle sizes, lower rates of dementia, and better memory function in a subpopulation of the Einstein Aging Study including Ashkenazi Jewish participants (n=124).

A similar effect was seen in a study of 593 racially and ethnically diverse participants from the Einstein Aging Study with VV homozygotes exhibiting a slower decline in memory on the Free and Cued Selective Reminding Test (FCSRT) relative to II homozygotes (difference in linear age slope 0.22, 95% Confidence Interval [CI] 0.02 to 0.41; P=0.03) [13]. Those with the VV genotype also had lower rates of all-cause dementia (Hazard Ratio [HR] 0.28, 95% CI 0.10 to 0.85; P= 0.02) and Alzheimer's disease (AD) (HR 0.31, 95% CI 0.10 to 0.95; P=0.03). Of note, this cohort contains a relatively high proportion of participants with Ashkenazi Jews ancestry (30%), and African American participants (25.6%). The majority of studies assessing the impact of CETP variants have used European Caucasian or Asian populations. The frequency of the V allele appears to be higher in African and possibly also Ashkenazi Jewish populations [2; 14], which may have increased the ability to detect an effect, and/or could be indicative of a selective advantage of the V allele in these groups.

A meta-analysis of 32 studies found no overall difference in the levels of I405V, C-629A, and Taq1B SNPs, which have been associated with reduced CETP levels, between Alzheimer's disease (AD) patients and controls [9]. In subgroup analysis, the B2B2 Taq1B genotype was higher in AD patients relative to controls in ApoE4 carriers in Asian populations (Odds Ratio [OR]: 3.46, 95% CI 1.57 to 7.60; p = 0.002). A separate meta-analysis including nine case-control studies in Caucasian and Asian populations (2,172 AD patients and 8,017 controls) found that the I405V CETP variant (rs5882 A>G) may increase the risk of AD (A allele vs. G allele: OR: 1.11, 95% CI 1.02 to 1.21; p=0.014), with the association primarily driven by

Caucasian populations [15]. A study of two prospective cohorts of the Danish general population (n= 102,607) found that genetic variants resulting in CETP deficiency were associated with a lower risk for vascular dementia (HR: 0.75, 95% CI, 0.58 to 0.95) [16]. Overall, there isn't a clear effect of CETP on dementia risk. The effect of CETP variants on dementia risk appears to be highly influenced by the genetic environment, particularly the presence of variants in other genes involved in cholesterol transport or metabolism, such as ApoE (see below). Additionally, it has been suggested that due to changes in cholesterol metabolism in the context of AD, the effects of these gene variants may be diminished by the disease-related pathological processes [17].

***Human research to suggest benefits to patients with dementia***:

CETP inhibitors have not been clinically tested in dementia patients.

***Mechanisms of action for neuroprotection identified from laboratory and clinical research***:

***Brain structure***: Observational studies have found that different variants in CETP are associated with differences in brain microstructure, and these associations may impact susceptibility to neurodegenerative diseases. A study including 403 Caucasian young adults (23.8±2.4 years) found an association between the I405V (rs5882 G>A) CETP variant and fractional anisotropy, an MRI measure of white matter integrity [18]. The presence of the V allele was associated with higher fractional anisotropy and lower diffusivity in young adults, indicative of better white matter integrity. However, this association was age dependent, such that the opposite trend was seen in a subset of older adults (74.3±7.3 years) from the ADNI cohort (n=78), whereby the V allele was associated with lower fractional anisotropy. This suggests that the impact of genes involved in cholesterol metabolism may vary with age, such that variants associated with better brain function and structure early in life may increase vulnerability to neurodegenerative disease in the context of aging-related brain changes. Meanwhile, a study including 52 middle-aged to elderly (age 51 to 85) Caucasian adults found that the V allele was associated with higher fractional anisotropy in the left temporal lobe in ApoE4 carriers, whereas those with the II genotype showed higher diffusivity and evidence of possible gray matter abnormalities in the gray matter of posterior brain regions [19]. The differences between the studies could be related to differences in the impact of CETP variants in different brain regions. Another study using participants from the ADNI cohort (n=318 MCI and n=188 controls) found that the I405V V allele was associated with a thicker parahippocampal cortex in ApoE4 carriers [10]. But this association was reversed in ApoE4 non-carriers. An ApoE4-depenent trend was also seen with the CETP C-629A variant, in which the A allele

was associated with a thinner parahippocampal cortex in ApoE4 non-carriers, but a thicker parahippocampal cortex in ApoE4 carriers. Both variants have been linked to reduced CETP activity and higher HDL levels in other studies, although the impact of these variants on brain and blood lipid profiles was not assessed in participants in these studies.

***Lipid profile:*** CETP is primarily thought to influence cognitive performance and the risk for cognitive decline by impacting the lipid profile in the blood and brain. In a study including 351 AD patients and 338 controls, the L/C/V CETP haplotype at the -1946 VNTR, C-629A and I405V SNPs was associated with higher CSF levels of lathosterol, a surrogate marker for *de novo* cholesterol biosynthesis, and 24S-hydroxycholesterol, the major cholesterol elimination product in the brain, which could be a sign of increased cholesterol turnover in the brain [17]. Notably, this association was only seen in the healthy control participants. Since CSF levels of these markers are lower overall in AD patients, indicative of a defect in brain cholesterol turnover, the effect of the CETP lowering gene variants may be obscured by the ongoing diseases processes in the context of AD. This highlights how the effect of altering CETP via genetic or pharmacological means may be impacted bythe context of different physiological and pathophysiological conditions. Serum levels of CETP were found to be elevated in diabetic patients with MCI (n=190) [20]. Elevated serum CETP levels were found to be associated with increased risk for cognitive impairment in diabetic patients with disordered lipid metabolism characterized by high LDL (≥2.59 mmol/L), high triglycerides (≥1.7 mmol/L), or low HDL (≤1.0 mmol/L for men and ≤1.3 mmol/L for women). Additionally, serum CETP levels were inversely associated with cognitive performance on the MoCA ($r = -0.638$; $p < 0.001$) and Auditory Verbal Learning Test ($r = -0.266$; $p = 0.008$), in this population. Lifestyle differences in conjunction with gene variants in other lipid-associated proteins may also play a role in these associations. A study assessing individuals over age 50 from rural and tribal populations of Dharmapuri District, India (n=187) found that the B2 allele of the CETP Taq1B variant influenced total cholesterol and LDL levels as well as with memory symptoms in the tribal population [21]. While the prevalence of the CETP variant was similar in the tribal and rural populations, variants in ApoE and LPL differed, and the combination of variants in these genes was found to impact lipid profiles. Additionally, lifestyle factors including obesity (body mass index) also affects lipid profiles, such that the higher prevalence of overweight individuals in the rural population may obscure or mitigate the impact of CETP on the blood lipid profile. As such, the association between CETP and cognition appears to stem from the degree to which CETP influences lipid profiles, in relation to other contributing genetic or lifestyle factors.

Due to the invasive nature of such measurements, human studies have generally not assessed the impact of CETP modulation on the lipid composition of the brain. Similar to the biomarker profile of

humans with variants expressing CETP at different levels, mice, which naturally lack CETP, expressing human CETP showed evidence of altered brain cholesterol and clearance. These mice had elevated levels of brain cholesterol (up to 22%) in response to a high-cholesterol diet, along with elevated levels of the cholesterol transporter ABCA7 [7]. The increase in brain cholesterol may stem from defective clearance and the accumulation of cholesterol within neurons, as suggested by a decrease in the production of 24S-hydroxycholesterol and increase in complement C1q. This was accompanied by an increase in peripheral pro-inflammatory cytokines, including TNFα and IL-1β.
The effect of CETP on brain cholesterol metabolism may underlie its link to AD risk [22]. While genetic variants can influence CETP activity in both central and peripheral compartments, the potential impact of CETP inhibitors on the central compartment is unclear.

***APOE4 interactions***:

CETP and ApoE are both involved in cholesterol transport and metabolism, and variants in both genes have been implicated in dementia risk. While ApoE4 is clearly associated with increased AD risk, the impact of CETP variants has been mixed across studies in different populations, suggesting that the effect of modifying CETP activity is highly dependent on the overall gene expression profile. In particular, many studies have found that the effect of CETP variants on brain lipids and dementia risk is modified by the ApoE genotype.
In a case-control study including participants from the Rotterdam study (544 AD cases and 5,404 controls), ApoE4 non-carriers with the VV genotype for the I405V allele were found to have an increased risk for AD (OR: 1.67, 95% CI 1.11 to 2.52, p = 0.01) [23]. Longitudinal cohort studies have found that the V allele may offer a protective advantage specifically in ApoE4 carriers. In a population of 909 participants from the Einstein Aging Study, the decline in memory, based on the picture version of the FCSRT with immediate recall, was modified in relation to the presence of the CETP I405V gene variant in ApoE4 carriers. ApoE4 carriers with the II genotype showed faster rates of memory decline relative to ApoE4 non-carriers, while ApoE4 carriers with the VV genotype did not show this accelerated rate of decline [14]. Meanwhile, the CETP genotype did not significantly affect rates of memory decline in ApoE4 non-carriers. Similarly, in the Cache County Study, including 4,486 participants, with up to 12 years of longitudinal cognitive assessments, the presence of each additional V allele in the I405V CETP variant slowed the annual average decline in cognitive function by 1.1 points in ApoE4 carriers [24]. There was a moderate protective effect of the V allele in ApoE4 non-carriers, with an average slowing of decline by 0.4 points.

In a case-control study from Spain including 286 AD patients and 315 controls, homozygosity for the C-629A variant (AA) (OR: 2.33, 95% CI 1.01 to 5.37) was associated with an approximately three-fold lower risk for AD in ApoE4 carriers relative to those without the variant (CC genotype) (OR: 7.12, 95% CI 4.51 to 11.24) [22]. In a case-control study from Germany including 163 patients with vascular dementia and 452 age-matched controls, ApoE4 non-carriers with AA genotype at the C-629A variant were found to be at an increased risk for vascular dementia (OR: 1.912, 95% CI 1.104 to 3.311) [25].
In a case-control study including 107 AD cases and 115 age-matched controls from a Northern Han Chinese population, the presence of the CETP D442G variant (G allele) showed a trend toward a reduced incidence of AD only in ApoE4 carriers [26]. The presence of the G allele was associated with a reduction in CETP activity (by 15-40%) and an elevation in HDL levels, suggesting that this variant, which is common in examined Asian populations, has a functional effect.
A key consideration to these studies is that these genetic variants alter CETP activity over the life course. It has not been established whether there is a particular stage of life when the differences in CETP activity most meaningfully impact cognitive outcomes and future dementia risk. Consequently, it is unclear whether taking CETP inhibitors starting in middle age or late life would be sufficient to phenocopy the protective effects seen with the genetic variants.

**Aging and related health concerns:** Potential cardiovascular benefits of cetrapibs are likely related to lowering LDL-C rather than raising HDL-C. Consistent benefits have not yet been seen with cetrapibs in Phase 3 RCTs.

*Types of evidence:*

- 2 meta-analyses of case-control studies for CETP gene variants and cardiovascular disease
- 2 meta-analyses of cetrapib RCTs with risk for newly onset diabetes
- 1 meta-analysis of case-control studies for CETP gene variants and longevity
- 1 meta-analysis of population-based studies for CETP gene variants and HDL-C levels
- 1 meta-analysis of case-control studies for CETP gene variants and age-related macular degeneration
- 1 systematic review of cetrapib RCTs and lipid profile changes
- 2 reviews of CETP gene variant-diet interactions
- 2 Mendelian randomization studies for CETP gene variants and cardiovascular measures
- 2 Mendelian randomization studies for CETP gene variants and breast cancer risk
- 4 Phase 3 clinical trials for cetrapibs

- 3 Phase 2 clinical trials for obicetrapib
- 7 cohort studies for CETP gene variants and longevity
- 2 case-control studies for CETP gene variants and intracerebral hemorrhage
- 1 prospective cohort study for CETP gene variants and age-related macular degeneration
- 3 observational studies for CETP gene expression and cancer prognosis

**Longevity:** ASSOCIATION BETWEEN CETP GENE VARIANTS WITH LONGEVITY IN CERTAIN POPULATIONS
The link between reduced CETP activity and longevity stems from a study in an Ashkenazi Jewish population [27]. However, the majority of studies using larger, more diverse populations have not shown a similar association for CETP variants and longevity. Furthermore, the same CETP variants have been inversely associated with longevity in some Asian populations [28], suggesting that the effect of CETP on lifespan is context-dependent with respect to genetic background and other environmental factors.
In a cohort of Ashkenazi Jewish individuals with exceptional longevity (n=213; age 98.2±5.3 years) and their offspring (n = 216; age 68.3±6.7 years), as well as an age-matched control group of Ashkenazi Jews (n = 258) and control group including participants from the Framingham Offspring Study (n = 589), HDL and LDL particle sizes were found to be significantly larger in the longevity group and their offspring, relative to the control groups [27]. The increase in lipoprotein particle size was found to be associated with reduced serum CETP levels and the presence of the V allele at the CETP I405V variant. Individuals with exceptional longevity and their offspring were found to have a 2.9- and 3.6-fold increased frequency of the VV genotype in men and 2.7- and 1.5-fold increased frequency of the VV genotype in women respectively, relative to control groups.
Associations of the I405V CETP variant with longevity were not seen in an Italian cohort (175 centenarians and 189 controls) [29], a Greek cohort (190 nonagenarians, 12 centenarians and 105 middle-aged controls) [30], or two Danish cohorts (n=1,088; age 92–93) (n= 1,281; age 94–100) [31].
A case-control study in Han Chinese participants including 506 with exceptional longevity and 515 controls found that the I405V V allele was inversely associated with longevity in this population [28]. Similarly, a meta-analysis of eight case-control studies (2,321 longevity subjects and 2,080 controls) also found that the I405V variant was associated with a lower incidence of longevity (OR: 0.81, 95% CI 0.74 to 0.88), and that this association was driven by East Asian populations [28]. Another study including 276 centenarians and 301 matched controls from Hainan, an island province in the South China Sea, found that the Taq1B B1B1 genotype (OR: 0.148, 95% CI 0.095 to 0.230) and I405V VV genotype (OR: 0.353, 95% CI 0.237 to 0.525) were inversely associated with longevity, and that the B2B2-II genotype was present only in the centenarian group [32].

A longevity study in Greece including three generations of long-lived families (n=85) with parents ≥90 years old and two generations of short-lived families (n=65), in which both parents died at ages younger than 75, assessed the association between proposed longevity-related SNPs and serum biomarkers [33]. CETP levels were found to be lower in individuals from long-lived families with the CETP Taq1B B2B2 genotype.

**Cardiovascular disease**

Observational studies linking low HDL-C levels with cardiovascular disease spurred the development of therapeutics aimed at raising HDL-C, including CETP inhibitors. However, evidence from both gene association studies and RCTs has called into question whether the level of HDL-C plays a causal role or whether it is acting as a surrogate for another factor which is driving the association with cardiovascular disease [34].

Depending on the context, CETP plays roles in activities that are considered both cardioprotective and atherogenic [35]. This may underlie the variability in responses to CETP variants and CETP inhibitors in diverse populations. CETP participates in the process of reverse cholesterol transport, in which excess cholesterol is transported out of peripheral tissues to the liver for excretion [36]. Small dense HDL particles can serve as cholesterol acceptors. CETP catalyzes the exchange of cholesterol esters for triglycerides from LDL and VLDL particles, thereby converting large buoyant HDL particles into small dense ones, which can then take up additional cholesterol from tissues. Because CETP inhibition prevents this transfer, it shifts the profile of HDL particles toward a larger size. Whether large or small HDL particles are indicative of a more favorable profile depends on the context [36]. In a well-functioning system, a higher level of large HDL particles could be indicative of higher levels of reverse cholesterol transport, whereas in a pathological context, it could be indicative of impaired clearance to the liver. The reason that CETP inhibition is considered cardioprotective is related to the transfer of cholesterol from HDL to atherogenic ApoB-containing lipoprotein particles, such as LDL. As a result, the activity of CETP needs to be considered within the ecosystem of all of the other lipid transporting mechanisms in the body, such that the impact of modulating CETP may vary in different contexts [37]. A genetic and/or biomarker-defined context in which the inhibition of CETP inhibition would be most cardioprotective has not yet been established.

***Gene association studies***: CARDIOPROTECTIVE PROFILE ASSOCIATED WITH CETP VARIANTS

Various studies have found an association between CETP genetic variants and risk for some forms of cardiovascular disease. A meta-analysis including 13,677 individuals from population-based studies and

pravastatin RCTs found that the presence of the Taq1B B2B2 genotype was associated with 0.11 mmol/L higher levels of HDL-C and a reduced risk for coronary artery disease (CAD) (OR: 0.78, 95% CI 0.66 to 0.93), relative to those with the B1B1 genotype [38]. The Taq1B B2 variant (rs708272) was also associated with a 3.1 mg/dL per allele increase in HDL-C levels and reduced risk of myocardial infarction (age-adjusted HR: 0.76, 95% CI 0.62 to 0.94) in a prospective cohort of 18,245 women from the Women's Genome Health Study [39]. A meta-analysis of 45 studies including 20,866 cases and 21,298 controls from both Caucasian and Asian populations, found that the Taq1B B1 variant was associated with a higher risk for composite ischemic cardiovascular disease risk (OR:1.15, 95% CI 1.09 to 1.21) and lower levels of HDL-C (standardized mean difference: 0.50, 95% CI 0.36 to 0.65), though the relationship between the Taq1B variant and HDL-C levels was more consistent in Caucasian populations [40]. The rs3764261 (C>A) variant, located in the promoter region of CETP, has also been associated with an increased level of HDL-C by 0.02 mmol/L per allele based on a meta-analysis of 11,021 individuals from three studies [41].

However, Mendelian randomization studies have suggested that atherosclerotic cardiovascular disease may be causally linked with LDL-cholesterol (LDL-C) and triglycerides, such that the association with HDL-C may be mediated by its relationship with these other lipid particles [34]. A study of two prospective Danish cohorts (n= 102,607 participants) found that genetic variants which reduce CETP levels were associated with lower risk of cardiovascular morbidity and mortality (HR 0.91, 95% CI 0.85 to 0.98), and 47% (95% CI  25% to 309%) of the effect on ischemic heart disease and 39% (95% CI 22% to 234%) of the risk for myocardial infarction was mediated by the reduction of non-HDL-C [16]. A Mendelian randomization study (n=5,706) found that genetically lower levels of CETP were associated with lower levels of LDL-C −0.08 mmol/L (95% CI −0.08 to −0.07), Apo B −0.03 g/L (95% CI −0.03 to −0.03), triglycerides −0.09 mmol/L (95% CI −0.10 to −0.08), and Lp(a) −2.20 nmol/L (95% CI −2.70 to −1.71) [8]. It is hypothesized that the association between HDL-C and cardiovascular disease is largely mediated by the inverse association between HDL-C and atherogenic triglyceride-rich lipoproteins [34]. In contrast to the protective effect seen for ischemic cardiovascular events, such as stroke, these HDL-C raising CETP variants have also been associated with an increased risk for intracerebral hemorrhage. A gene analysis including 1,149 cases and 1,238 controls from three studies found that 12 CETP variants showed an association with intracerebral hemorrhage, with the rs173539 variant exhibiting the strongest association (OR: 1.25; $p = 6.0 \times 10^{-4}$) [42]. In a replication cohort including 1,625 cases and 1,845 controls from five studies, CETP variants which increased HDL-C (by ~2.85mg/dL) were associated with increased risk for intracerebral hemorrhage (OR:1.86; $p = 1.39 \times 10^{-6}$). Similarly, a Mendelian randomization study including participants from the UK Biobank (n= 1,545 cases, n=1,481 controls)

found that HDL-C raising CETP variants were also associated with increased risk for intracerebral hemorrhage (OR: 1.64, 95% CI 1.26 to 2.13) [43]. It is unclear whether the association is directly related to the change in HDL-C, or whether it stems from other changes to the overall lipid profile with these variants. A meta-analysis including 287,651 participants from 39 trials for lipid lowering agents suggests that it may be a combination, as there was no significant overall effect on intracerebral hemorrhage (OR: 1.12, 95% CI 98 to 1.28), but there was a modest increase in risk when including only secondary prevention trials (OR: 1.18, 95% CI 1.00 to 1.38) [44].

***CETP Inhibitors*:** NO CONSISTENT BENEFIT OF CETP INHIBITORS IN RCTS

Four CETP inhibitors, anacetrapib, dalcetrapib, evacetrapib, and torcetrapib, have been tested in Phase 3 clinical trials, but none were shown to reliably reduce adverse cardiovascular events [45]. A meta-analysis of 11 trials for anacetrapib, dalcetrapib, and evacetrapib (n = 62,431) found no overall effect of CETP inhibitors on major adverse cardiovascular events (MACE) (Relative risk [RR]: 0.97, 95% CI 0.91 to 1.04), risk of stroke, hospitalization due to acute coronary syndrome, revascularization, or all-cause mortality (RR: 0.95, 95% CI 0.89 to 1.02) [46]. There were non-significant trends toward reduced risk of nonfatal myocardial infarction and cardiovascular mortality, which were driven by the anacetrapib REVEAL trial (NCT01252953), which is the one trial to show a significant reduction (9%, 95% CI 3 to 15%; P = 0.004) in the incidence of major coronary events with treatment during the study period (median 4.1 years) (n=30,449), as well as a further 20% (95% CI 10 to 29%; P < 0.001) reduction during the (median 2.2 years) extended follow-up period (n=26,129) [47]. This has raised questions as to the duration of treatment with CETP inhibitors needed to see an impact on cardiovascular outcomes, and whether the follow-up periods of the other trials were too short to detect an effect [8].

All four drugs significantly raised HDL-C levels in clinical trials, suggesting raising HDL-C alone is not sufficient for cardioprotection. Evacetrapib and anacetrapib had the largest impact on HDL-C levels, increasing them by 132% (95% CI 130 to 133%), and 130% (95% CI 127 to 133%), respectively [8]. Torcetrapib increased HDL-C levels by 52% (95% CI 49 to 55%), while dalcetrapib increased HDL-C by 29% (95% CI 23 to 43%). While the trends were similar, they differed in their abilities to impact non-HDL-C levels. Anacetrapib and evacetrapib reduced LDL-C by −38% (95% CI −40 to −36%), and −37% (95% CI −38 to −36%), respectively, while torcetrapib reduced LDL-C by −20% (95% CI −24 to −17%), and dalcetrapib had a negligible effect on LDL-C (−1%, 95% CI −1.1 to −0.9%) [8]. It is thought that the potential cardiovascular benefit of anacetrapib in the REVEAL trial was related to its effects on non-HDL-C atherogenic ApoB-containing lipoproteins, including LDL-C, triglycerides, and Lp(a) [1]. It should be noted that the stated effects on LDL-C and other non-HDL-C ApoB-containing particles in these trials

may be overestimated due to technical reasons related to changes in particle composition with CETP inhibition.
Despite the failure of these clinically tested drugs, many consider the lack of efficacy to be compound-related, stemming from low potency or off-target side effects, rather target-related [1; 11]. As a result, novel CETP inhibitors are still being developed and tested.

Obicetrapib, formerly known as TA-8995, is currently in clinical development [48]. It is the most specific and potent clinically tested CETP inhibitor to date, showing up to 97% CETP inhibition. Based on the lack of clinical efficacy in relation to HDL-C elevation in prior CETP inhibitor trials, the studies with obicetrapib have focused on its ability to further reduce atherogenic ApoB-containing lipoproteins. In the TULIP trial, 364 patients with mild dyslipidemia were treated with 1, 2.5, 5, or 10 mg of obicetrapib, 10 mg of obicetrapib in combination with atorvastatin or rosuvastatin or placebo once daily for 12 weeks [48]. LDL-C, as measured by beta-quantification, was reduced by 45.3% with the 5 mg and 10 mg monotherapy doses, and by 68.2% and 63.8% with the statin combination treatment. ApoB levels were reduced by 33.6%, and 33.7% at the 5 mg and 10 mg doses, and by 50.1% and 46.3% with the combination [49]. Lp(a) levels were also reduced by 36.9% and 33.4% at the 5 mg and 10 mg doses of obicetrapib. In contrast to LDL-C reduction, where an additive effect was seen, the reduction of Lp(a) by obicetrapib was slightly mitigated to 25% in combination with statins. In the Phase 2 ROSE trial (NCT04753606), patients with dyslipidemia taking high-intensity statins (atorvastatin or rosuvastatin) (n=120) were treated with 5 mg or 10 mg obicetrapib for eight weeks [50]. Obicetrapib at the 5 mg and 10 mg doses reduced LDL-C levels from baseline relative to placebo, based on the Friedewald formula, by 42.9% and 45.7%, reduced ApoB levels by 24.4% and 29.8%, non-HDL-C by 38.9% and 44.4%, and Lp(a) by 33.8% and 56.5%, respectively. Individuals with the highest ApoB levels (> 100 mg/dL) showed the greatest reduction with obicetrapib treatment (39% from baseline). In the Phase 2 ROSE2 trial (NCT05266586), patients with dyslipidemia taking high-intensity statins (n=97) were treated with 10 mg obicetrapib as monotherapy or in combination with the Niemann-Pick C1-Like 1 inhibitor, ezetimibe, for 12 weeks [51]. Obicetrapib reduced LDL-C by 43.5% as a monotherapy and by 63.4% in combination, compared to a 6.35% reduction with placebo, as measured by the Friedewald calculation. There was also a change in the distribution of particle sizes toward larger particles, driven by the reduction of small LDL particles by 95.4% and 92.7%, with monotherapy and combination therapy, respectively. Small LDL particles are thought to be especially atherogenic due to their rapid oxidation and ability to penetrate vascular tissue. Non-HDL-C levels were reduced by 55.6% and 37.5%, while ApoB levels were reduced by 34.4% and 24.2%, with monotherapy and combination therapy, respectively. The overall change in lipid profile is consistent with obicetrapib increasing cholesterol flux through the HDL fraction. Obicetrapib is

currently being tested in the Phase 3 PREVAIL (NCT05202509) and BROADWAY (NCT05142722) trials in patients with atherosclerotic cardiovascular disease, and the BROOKLYN (NCT05425745) trial in patients with a history of heterozygous familial hypercholesterolemia.

Another reason why raising HDL-C levels in patients with cardiovascular risk factors may not lead to the type of cardioprotection seen in observational studies stems from the heterogeneity of HDL particles, which is not adequately captured by focusing solely on HDL-C [52]. Numerous subspecies of HDL particles have been identified which differ in terms of their size, content, and functionality. HDL particles can vary in terms of the composition of associated lipids, proteins, and miRNAs, which in turn, can influence HDL function. Depending on the subspecies, HDL particles can exert pro- or anti-inflammatory actions, and thus depending on the context, may be considered either pro- or anti-atherogenic. As a result, the impact of raising HDL-C levels likely depends on the milieu of HDL particles in a given individual and which ones are preferentially affected. High HDL-C levels may be associated with cardioprotection in healthy individuals because they have high levels of protective HDL particles, whereas in patients with a dysfunctional HDL profile at baseline, raising HDL-C without improving the HDL profile is unlikely to be beneficial, and could potentially further exacerbate lipid dysfunction. One study analyzed the impact of evacetrapib and torcetrapib on HDL profiles, based on a subset of 126 patients from the ACCENTUATE and 80 patients from the ILLUMINATE trials, respectively [53]. Both drugs increased ApoA1 in HDL species containing ApoC3. ApoC3 has been associated with coronary heart disease risk. The ApoA1-ApoE complex on HDL is considered cardioprotective, however, this protective effect is blunted by the copresence of ApoC3. Torcetrapib increased ApoA1 on HDL containing only ApoC3 by 96%, and those containing both ApoC3 and ApoE by 43%, but did not significantly raise levels of those containing only ApoE, suggesting a selective increase of atherogenic subspecies. Evacetrapib also increased the concentration of ApoA1 on HDL species containing proteins associated with inflammation such as fibrinogen, and complement C3, though it also increased ApoA1 on species associated with antioxidation. The increase in ApoA1 on HDL species involved in lipid metabolism may stem from changes in the lipid content of the particles due to CETP inhibition. While both the relative and absolute levels of the different HDL subspecies likely contribute to the overall cardiovascular risk profile in an individualized manner that has not yet been characterized, this study suggests that CETP inhibitors may be altering the subset of HDL particles is a less favorable manner.

In addition to the genetic background, the impact of CETP inhibition may depend on lifestyle factors, such as diet, exercise, and comorbid disease. The profile of plasma lipids of individuals with CETP variants in response to particular dietary interventions was found to be variable in study populations

from different ethnic groups [2]. In some cases, changes to lipid profiles in those with CETP variants were more pronounced in response to a high fat diet, while in other cases, lipid profiles were more affected by a high sugar diet. Some of the differences may also have been related to the types/sources of fats preferentially consumed in different parts of the world. As a result, CETP variants may primarily impact blood lipid profiles by modifying the response to diet [2]. A similar modifying effect of diet in relation to the effect of CETP activity has been seen in rodent studies [35]. In rats, the presence or absence of CETP had different effects on lipoprotein profiles in response to different diets. Non-HDL-C was elevated in response to a high-fat diet regardless of CETP genotype, but only in CETP expressing rats in response to a high-sugar diet. Certain foods, such as legumes, fish, and olive oil, have also been associated with reducing the activity of CETP [37]. Therefore, one's baseline diet and genetics may act synergistically on CETP activity. Dietary components, such as polyphenols, and exercise have been associated with improving the antioxidant and cholesterol export functionality of HDL particles [37; 52]. These may, in turn, impact the potential protective effect of raising HDL-C.

A study including 534 participants from the DEFINE RCT testing 100 mg anacetrapib for 18 months in patients with coronary artery disease assessed the effect on macrophage cholesterol efflux [54]. Anacetrapib treatment was associated with an increase in macrophage cholesterol efflux, but only in men, and was related to the change in ApoB levels. In patients with diabetes, the effect was modified by the haptoglobin genotype. Haptoglobin is an HDL-associated protein that prevents oxidative damage. The haptoglobin 2-2 variant lacks this protective activity, and is instead associated with increased oxidation and risk for cardiovascular disease [55]. The increase in cholesterol efflux with anacetrapib was only seen in those with the 1-1 genotype [54].

The profile of ApoB-containing particles may also affect the protective potential of CETP inhibition. CETP activity is affected by the surface and core features of ApoB-containing lipoproteins involved in the transfer of cholesterol esters [20]. Individuals with type 2 diabetes were found to have increased serum levels of CETP in response to abnormalities in ApoB-containing LDL and VLDL particles [20].

Overall, these studies suggest that the impact of modulating CETP activity on cardiovascular risk factors is complex, involving the interaction of genetic and lifestyle factors, which could result in variable responses across individuals.

**Diabetes**: ASSOCIATION FOR DECREASED RISK IN CETP INHIBITOR RCTS

Although CETP inhibitors did not appear to show preferential benefit for patients with diabetes, meta-analyses from clinical trials suggest that treatment with CETP inhibitors may reduce the risk of newly onset diabetes. This is notable because other lipid-lowering drugs, such as statins, have been associated with increased risk for diabetes [56]. A meta-analysis of four RCTs including 73,479 patients found a 12%

reduction in the incidence of diabetes with CETP inhibitor treatment (OR: 0.88, 95% CI 0.81 to 0.96) [57]. Another meta-analysis of four RCTs (n= 75,102) found that CETP inhibitor treatment was associated with a 16% reduction in the risk of newly onset diabetes (RR: 0.84; 95% CI 0.78 to 0.91) [11]. There were also trends toward improvement on glycemic measures, including plasma fasting glucose, insulin, HbA1c, and HOMA-IR. In the dal-OUTCOMES trial with dalcetrapib, there were reductions in the transition from normoglycemia to prediabetes, and from prediabetes to diabetes, as well as an increase in the reversal from diabetes to normoglycemia [58]. However, in the ACCELERATE trial, diabetes patients remained at elevated risk for adverse cardiovascular events, despite significant changes to the lipid profile in response to evacetrapib treatment [59]. That dalcetrapib, which shows much lower potency relative to evacetrapib, led to a stronger effect on diabetes parameters suggests that the effect of CETP inhibitors on diabetes may be tied to activity unrelated to changes in LDL-C [11]. Instead, the effects may be related to CETP's associations with pancreatic cell survival and insulin secretion [57].

**Age-related macular degeneration**: POTENTIAL ASSOCIATION WITH CETP GENE VARIANTS
Gene association studies have linked HDL-raising variants, including CETP variants, with increased risk for age-related macular degeneration (AMD). A meta-analysis of five European cohorts including 2,267 AMD cases and 4,266 controls found an association between very large HDL particles and AMD risk (OR: 1.12, 95% CI 1.05 to 1.20) [60]. The rs17231506 (C>T) variant, which is associated with increased HDL-C levels, was associated with increased AMD risk, whereas the rs5817082 the (C>A) shows the opposite pattern, with lower levels of HDL-C and reduced AMD risk. Gene variants related to CETP deficiency and increased HDL-C levels have also been associated with increased risk for AMD in a study of prospective Danish cohorts (n= 102,607) (HR: 1.24, 95% CI 1.11 to 1.39), which was attributed to the elevation in HDL-C levels in mediation analysis [16]. Since AMD and cardiovascular disease tend to show similar risk factors, this opposite trend in relation to HDL-C and CETP is difficult to interpret. It may be related to the role of lipid and cholesterol dysregulation in the formation of drusen, the lipid and protein containing deposits under the retina. One study examined whether individuals with soft drusen and those with subretinal drusenoid deposits have different forms of AMD [61]. These different types of drusen have different lipid profiles, and may confer different risks for disease progression, with the subretinal deposits associated with more severe retinal degeneration. The study found that the presence of subretinal drusenoid deposits was associated with classical cardiovascular disease risk factors, such as low HDL-C, while the form with only soft drusen was associated with CETP variants that raise HDL-C. The relationship between HDL-C and AMD may also be related to HDL particle composition. Complement activity has been associated with AMD [62], such that the risk could be related to increases in the levels of complement-containing HDL particles [60].

At this point, the risk for AMD with CETP inhibitors is theoretical, as the RCTs testing CETP inhibitors have not shown evidence of increased cases of AMD [16]. Though, it should be noted that AMD can take years to develop, such that the follow up periods may not have been long enough to detect a change. Additionally, the potential impact on AMD may be influenced by the duration of CETP inhibition, such that an impact may not become apparent in the absence of chronic long-term dosing.

**Cancer:** ELEVATED CETP IS ASSOCTIAED WITH WORSE PROGNOSIS IN SOME CANCERS
Similar to cardiovascular disease, low levels of HDL-C have been associated with some forms of cancer [63]. A meta-analysis of RCTs for lipid-altering interventions concluded that the risk for cancer is reduced by 36% for every 10 mg/dL increase in HDL-C [64]. However, the relationship between cancer and HDL-C appears to be complex and tumor-type dependent. The role of CETP in this relationship is also unclear, but is likely to be context dependent. There is some preclinical evidence to suggest that CETP inhibitors may help reduce cancer cell viability for some tumor types, but it has not been established how they might impact cancer incidence rates.
In colorectal cancer, high HDL-C levels have been associated with decreased risk and increased survival [63]. Colorectal cancer patients show evidence of a shift towards smaller size HDL particles, which is consistent with increased CETP activity within tumor tissue [63].
CETP expression was found to be elevated in breast cancer tissue and low levels of CETP were associated with better long-term survival [65]. In cell culture, CETP inhibition or knockdown reduced the growth rate of MCF-7 breast cancer cells [65]. However, Mendelian randomization studies have found that CETP variants that raise HDL-C levels were associated with increased risk for breast cancer [66; 67].
A bioinformatic database analysis found that high expression of CETP was associated with worse prognosis and survival in patients with gastric cancer [68].
A meta-analysis of genome-wide association studies (GWAS) found that CETP variants were not associated with risk for head and neck cancer [69].

**Safety:** Cetrapibs have been well-tolerated in clinical trials with adverse event profiles largely similar to placebo, though some show elevations on an inflammation marker. Blood pressure elevations with torcetrapib were related to off-target effects.

*Types of evidence:*

- 1 meta-analysis of RCTs testing cetrapibs
- 1 meta-analysis of RCTs for anacetrapib

- 1 meta-analysis of RCTs for evacetrapib
- 4 Phase 3 RCTs testing cetrapibs
- 3 Phase 2 RCTs testing obicetrapib
- 1 Phase 1 RCT testing MK-8262

CETP inhibitors were generally well-tolerated in clinical trials, with most adverse events classified as mild to moderate. Based on a meta-analysis of 12 RCTs (n = 2,928), the most commonly reported adverse events with CETP inhibitors were headache, fecal abnormalities, diarrhea, and infection [70].

***Torcetrapib*** was associated with increases in systolic and diastolic blood pressure, due to its effects on aldosterone [71]. The Phase 3 ILLUMINATE trial was terminated early due to a 0.4% absolute increase in the mortality rate (93 vs 59) and 1.2% increase in the MACE rate (464 vs 373) in the torcetrapib treated group [71; 72]. A proteomics sub-study from this trial including 249 patients treated with torcetrapib plus atorvastatin compared to 223 patients receiving atorvastatin alone found that within three months of torcetrapib treatment, 76% of altered plasma proteins changed in a direction associated with increased cardiovascular risk [72]. These included proteins involved in immune function, inflammation, and aldosterone function. Torcetrapib treatment was associated with a reduction in the level of potassium and an increase in levels of sodium, bicarbonate and aldosterone [71]. These cardiovascular adverse effects of torcetrapib were largely attributed to its off-target effects on aldosterone, and were not seen in the context of other CETP inhibitors.

***Anacetrapib*** was not associated with increased incidence of hepato-toxicity, musculoskeletal injury, drug-related adverse events, or drug-related trial withdrawal relative to placebo in a meta-analysis of ten trials including 34,781 participants [73]. Anacetrapib treated patients in the Phase 3 REVEAL trial have been assessed in the longest follow-up to date, with a median of six years (n=26,129) [47]. In this study, there were fewer deaths from cardiovascular causes in patients allocated to anacetrapib (4.7% (n=722) vs. 5.2% (n=796); P = 0.05), but no overall effect on non-vascular mortality. Additionally, there were no differences with respect to cancer rates or serious adverse events with anacetrapib. Despite the positive impact on cardiovascular-related mortality, clinical development of anacetrapib was halted due to its pharmacokinetic properties, as it has poor aqueous solubility, CYP3A4-inducing activity, pregnane X receptor inhibition ($IC_{50}$ of 3.5 µM *in vitro),* a long terminal half-life, and adipose tissue accumulation with chronic dosing [3].

***Dalcetrapib*** was generally well-tolerated in clinical trials. In the Phase 3 dal-OUTCOMES trial (n=15,871), hypertension was more common in the dalcetrapib treated group, with mean systolic blood pressure remaining approximately 0.6 mmHg higher in the treated group, relative to placebo, although there were no effects on diastolic blood pressure or on measures of plasma aldosterone, potassium, or bicarbonate [74]. There were also increased incidences of diarrhea (563 patients vs 358 patients) and insomnia (169 patients vs 133 patients) with dalcetrapib. Additionally, median C-reactive protein levels were 18% higher in the dalcetrapib-treated group following three months of treatment (1.6 mg/L vs 1.4 mg/L). Incidence rates of cancer and infections were similar across groups, and dalcetrapib was not associated with significant changes to hepatic function, renal function, or creatine kinase levels. It was noted that the response to dalcetrapib may be influenced by genetic background, particularly, the rs1967309 SNP in the ADCY9 gene. In the dal-OUTCOMES trial, the AA genotype was associated with a 39% reduction in cardiovascular events in response to dalcetrapib, whereas the GG genotype was associated with a 27% increase in adverse cardiovascular events [75]. There was a similar effect seen with evacetrapib, but it was not consistent across trials, thus it is not clear whether this association is CETP-related, drug-related, or a chance association. This association will be further examined in the upcoming the Phase 3 dal-GenE-2 trial (NCT05918861).

***Evacetrapib*** was not associated with an increased incidence of adverse events, serious adverse events, or adverse events leading to discontinuation relative to placebo in a meta-analysis of five RCTs including 12,937 participants [76]. Evacetrapib was also not associated with increased incidence for liver enzyme (creatinine kinase and alanine aminotransferase) elevations, and was associated with a lower overall incidence of death relative to placebo (RR: 0.84, 95% CI 0.71 to 0.99). In the Phase 3 ACCELERATE trial (n=12,092), evacetrapib was associated with a slightly increased incidence of hypertension relative to placebo (11.4% vs. 10.1%, P=0.02), as well as a greater increase in the levels of the inflammatory biomarker high-sensitivity C-reactive protein (8.6% [interquartile range −27.0 to 63.3] vs. 0% [interquartile range −32.1 to 52.4], P<0.001 [77]. In the subset of patients with diabetes in the Phase 3 ACCELERATE trial (n=8,236), there was a small, but statistically significant increase in the incidence of acute pancreatitis in patients treated with evacetrapib (13/3699 vs 3/3678) [59].

***Obicetrapib*** is the most polar of the clinically tested cetrapibs, which allows for greater bioavailability at lower doses. Obicetrapib has generally been well-tolerated in clinical trials. In the Phase 2 TULIP trial (n=364), there was no significant effect of obicetrapib up to 10 mg as monotherapy or in combination with atorvastatin on laboratory safety parameters including serum aldosterone, salivary cortisol, high-sensitivity C-reactive protein, endothelin-1, serum electrolyte concentrations, blood pressure or HOMA-

IR [49]. The most common adverse events with obicetrapib were nasopharyngitis and headache. In the Phase 2 ROSE trial (n=120) in which obicetrapib (5 or 10 mg) was tested on the background of high-intensity statins, the most common adverse events were gastrointestinal disorders, nausea, and headache, though rates were largely similar between obicetrapib and placebo groups [50]. Adverse events were generally mild and moderate, and most were not considered drug related. There were no clinically meaningful changes in laboratory parameters or vital signs. In the Phase 2 ROSE2 trial (n=97), in which 10 mg obicetrapib was tested in combination with ezetimibe and statins, the most common adverse events were nausea, urinary tract infection, and headache, which were generally mild to moderate severity, with similar incidence rates across groups [51]. There were no clinically meaningful changes to laboratory biochemical parameters or vital signs. Plasma levels of obicetrapib steadily decreased with drug cessation, with no evidence of accumulation in adipose tissue.

***MK-8262*** was tested in a Phase 1 clinical trial in healthy volunteers and was found to be well tolerated in single oral doses up to the highest tested dose, 90 mg [3]. It had a half-life of approximately 120 hours, and in contrast to anacetrapib did not show evidence of a food effect or adipose tissue accumulation.

***Drug interactions***: The major interactions with CETP inhibitors are likely to be drug specific. The CETP inhibitors still in clinical development, dalcetrapib and obicetrapib, have not been shown to have major drug interactions with other drugs commonly used in the treatment of cardiovascular disease, such as ezetimibe and statins, and have been safely used in combination with these classes of drugs in RCTs [51; 78]. Dalcetrapib did show an interaction with the lipase inhibiting weight loss medication, orlistat [78].

**Sources and dosing:**

To date, none of the clinically tested CETP inhibitors have been approved for any indication. Clinical development of anacetrapib, evacetrapib, torcetrapib, and MK-8262 has been discontinued. Dalcetrapib is currently being tested in a Phase 3 RCT sponsored by DalCor Pharmaceuticals at a dose of 600 mg/day, in the form of two 300 mg oral tablets (NCT05918861). Obicetrapib is currently being tested in Phase 3 RCTs sponsored by NewAmsterdam Pharma at an oral dose of 10 mg/day.

**Research underway:**

***Dalcetrapib*** will be tested in the Phase 3 dal-GenE-2 trial in a genetically defined population with a recent acute coronary syndrome (NCT05918861). The study will include participants with the AA genotype at variant rs1967309 in the ADCY9 gene. The estimated completion date is in 2027.

There are currently four active clinical trials for ***obicetrapib***.
Obicetrapib is being tested in two Phase 3 clinical trials in patients with inadequately controlled atherosclerotic cardiovascular disease, the PREVAIL (NCT05202509) and BROADWAY (NCT05142722) trials, which have estimated completion dates in 2026 and 2024, respectively.
Obicetrapib is being tested in the Phase 3 BROOKLYN trial (NCT05425745) in patients with a history of heterozygous familial hypercholesterolemia, which has an estimated completion date in 2024.
Obicetrapib is also being tested in a Phase 2 dose-finding study in Japanese patients to evaluate the effect of obicetrapib as an adjunct to stable statin therapy (NCT05421078), which has an estimated completion date in 2023.

**Search terms:**
Pubmed, Google: CETP INHIBITORS; CETP GENE VARIANTS

- Alzheimer's disease, neurodegeneration, cognition, longevity, cardiovascular disease, cancer, clinical trials, safety, meta-analysis

Websites visited for CETP Inhibitors:

- Clinicaltrials.gov (Anacetrapib, Dalcetrapib, Evacetrapib, Torcetrapib, Obicetrapib)
- PubChem (Anacetrapib, Dalcetrapib, Evacetrapib, Torcetrapib, Obicetrapib, MK-8262)
- DrugBank.ca (Anacetrapib, Dalcetrapib, Evacetrapib, Torcetrapib, Obicetrapib)
- Cafepharma (Anacetrapib, Dalcetrapib, Evacetrapib, Torcetrapib, Obicetrapib)

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